

## Understanding the Pathophysiology of Neonatal Jaundice

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Bilirubin mainly originates from heme via the catalyzation of heme oxygenase (HO) and biliverdin reductase and is conjugated into direct form by UDP-glucuronosyl transferase (UGT1A1) for subsequent biliary secretion [1]. Jaundice develops when conjugated or unconjugated bilirubin deposits onto the skin. It is very common during the neonatal period. Neonatal jaundice is related to a variety of physiologic and pathologic conditions [2]. Physiologic aspects are comprised of increased bilirubin production, less efficient hepatic conjugation and enhanced enterohepatic circulation. In respect of pathologic situation, there are two patterns of diseases: hyperbilirubinemia and cholestasis. Hyperbilirubinemia refers to accumulation of unconjugated bilirubin beyond the extent of physiologic jaundice, while cholestasis results from the excretory obstruction of conjugated bilirubin.

Neonatal hyperbilirubinemia carries a potential risk of kernicterus, a long-term neurological impairment [3]. Proper management is of paramount importance to avoid the complications. The traditional therapy is phototherapy and exchange transfusion [4]. Phototherapy is the mainstay of treatment, with exchange transfusion held in reserve for neonates with bilirubin encephalopathy. Despite its potential harm, unconjugated bilirubin has been proposed as an antioxidant. HO and biliverdin reductase might also play roles in the protection from oxidative stress for vulnerable neonates [5,6].

Etiological verification is essential because the underlying diseases are critical factors of neurological sequelae [7]. There is a wide range of conditions that affect bilirubin levels, including environmental and genetic origins. These events may aggravate the destruction of red blood cells (e.g. cephalohematoma, hemolysis), delay the metabolism (e.g. prematurity) and increase the absorption of bilirubin (e.g. intestinal obstruction) [8]. Although breastfeeding is a major cause of neonatal hyperbilirubinemia, it does not serve as a risk factor for kernicterus [7,9]. Instead, sepsis carries the greatest risk of poor outcomes.

The most important maternal effect on neonatal hyperbilirubinemia is isoimmune hemolytic disease. The clinical manifestation is early-onset hyperbilirubinemia with anemia [10]. Rh incompatibility displays more severe hyperbilirubinemia than ABO incompatibility. With the introduction of Rh immunoglobulin, the incidence of Rh isoimmune hemolytic disease has declined. By far ABO incompatibility is the most common cause of isoimmune hemolytic disease.

A large number of evidence has shown a correlation of neonatal hyperbilirubinemia with genetic factors, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency and Gilbert syndrome (a genetic polymorphism of UGT1A1) [11]. G6PD deficiency is the most common genetic disorder in the world. Contact with naphthalene will induce neonatal hyperbilirubinemia in G6PD-deficient neonates [12]. Even in the environment free from agents that can potentially cause hemolysis, they are at greater risk of neonatal hyperbilirubinemia [13]. In addition, genetic interactions could enhance the severity of neonatal hyperbilirubinemia [11,14].

Jaundice persists beyond 14 days of life can be a sign of neonatal diseases [15]. Cholestasis, such as biliary atresia, should be considered. Prompt intervention is essential for identification of biliary atresia that

requires early operation. Nevertheless, the vast majority of neonates with prolonged jaundice are associated with breastfeeding. Both environmental and genetic factors are involved in the development of breast milk jaundice [16,17].

Causation of neonatal jaundice carries a geographic difference. Challenge exists in the determination of causation. With an enthusiastic support for breastfeeding, it has become a leading cause of neonatal hyperbilirubinemia. There are complex interrelationships between and within genetic and environmental factors. Clinicians need to develop a systematic approach to identify the possible etiologies in relation to neonatal jaundice.

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